THE IMPACT OF PULMONIC VALVE REPLACEMENT ON VENTRICULAR ARRHYTHMIAS ASSOCIATED WITH TETRALOGY OF FALLOT PATIENTS

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Abstract

Background: There is no consensus on the timing of pulmonary valve replacement (PVR) in these patients or the impact of PVR on the subsequent development of fatal arrhythmias such as ventricular tachycardia. We have assessed the incidence of ventricular arrhythmias in patients with PVR versus those without PVR in patients with TOF. Methods: We performed an aggregate data meta-analysis on 12 studies with 1,740 patients on the development of ventricular arrhythmias following initial repair, comparing patients who had PVR years after initial repair versus those who had no further intervention. We also performed a meta-regression analysis to evaluate the effect of preoperative and postoperative right ventricular end-diastolic volume (RV-EDV) and QRS on the incidence of ventricular arrhythmias. Results: Among 1,740 patients with TOF, ventricular arrhythmias in patients with PVR were reduced by almost 60% than patients without PVR (OR 0.40, 95% CI 0.219-0.725, p <0.003). Similar results were noted in both fixed- and random-effects models. The standardized difference in means for RV-EDV after PVR showed a statistically significant reduction after PVR (random-effects model: -1.44, SE = 0.188, p < 0.0001). Patients also had a statistically significant increase in RV-EF and reduction QRS as well as increase in RV-EF following PVR. Neither pre-operative RV-EDV nor QRS duration was associated with statistically significant coefficients for changes in the incidence of VT by meta-regression. Conclusion: For TOF survivors after repair, there was a markedly reduced rate of ventricular arrhythmias in patients who received PVR compared to patients without PVR.

Introduction:

Data comparison between ventricular arrhythmias and Tetralogy of Fallot (TOF) has shown inconsistent results in terms of both incidence and mortality. There is no consensus on the timing of pulmonary valve replacement (PVR) in patients with TOF.[1–3]Currently, PVR after initial correction for Tetralogy of Fallot is indicated for symptomatic patients or those at risk for life-threatening arrhythmias. However for asymptomatic patients, there is still no consensus on the optimal timing of PVR.[1,4–8]Additionally, the impact of PVR on the subsequent development of fatal arrhythmias, such as ventricular tachycardias. is understudied.[1]The parameters Right ventricular ejection fraction (RVEF) <30%, left ventricular ejection fraction (LVEF) < 45%, and QRS duration >180ms have been shown to predict the development of ventricular tachycardia.[1]It remains unclear whether there is an association between preoperative RV volume/RV end-diastolic volume (RV-EF) and QRS duration on outcomes.[9,10]We aim to evaluate the association of PVR after initial corrective surgery for TOF and its relationship to the development of ventricular arrhythmias compared to patients who do not undergo PVR.

Methods:

Eligibility Criteria. With the PICOS (Participants, Interventions, Comparisons and Outcomes) strategy, studies were considered if: 1) the population comprised of patients with total repaired TOF and moderate pulmonary valve insufficiency; 2) patients evaluated for PVR; 3) patients assessed before and after PVR; 4) outcomes included indexed RV-EDV, RVEF, pulmonary regurgitation fraction (PRF), QRS, RV/LV ratio; and 5) studies were either prospective, retrospective, non-randomized, or randomized controlled trials.

Search Methods and Study Selection. A systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two co-authors (YSK and NRD) independently searched published studies indexed in OVID, Cochrane Central Register of Controlled Trials via the Wiley Interface, Web of Science Core Collection, MEDLINE, EMBASE, and Google Scholar from October 31, 2019 and updated in April 1, 2020 were searched thoroughly for the following keywords: "Tetralogy of Fallot"OR "Tetralogy, Fallot's" OR "Tetralogy, Fallot" OR "Tetralogy, Fallots" OR "Fallot's Tetralogy" OR "Fallot Tetralogy" OR "Fallot's Tetralogy") AND ("PulmonaryValve Insufficiency"OR"Valve Insufficiency, Pulmonary" OR "Regurgitation, Pulmonary" OR "Pulmonary Regurgitation" OR "Valve Regurgitation, Pulmonary" OR "Valve incompetence, Pulmonary" OR "Pulmonary Valve Incompetence" OR "Pulmonary Valve Regurgitation" OR "Regurgitation, Pulmonary Valve" OR "Insufficiency, Pulmonary Valve" OR "Pulmonary Valve Replacement" OR "arrhythmia/tachycardia" OR "tachycardia," OR "ventricular arrhythmias." We also performed extensive hand searching by screening references of included studies and review articles for additional citations.

Adverse events, such as cardiovascular mortality and events, were defined by the standards of the Common Terminology Criteria for Adverse Events.

Data extraction. Two co-authors (YSK and NRD) independently screened studies for inclusion. When there were differences in information for a trial, we included the most up-to-date data from ClinicalTrials.gov. In Excel, a data extraction table was utilized to compile and display the pertinent information from each article. The information was the following: first author's name, publication year, study design, sample size, and incidence and mortality from ventricular arrhythmias. The table was constructed by the first author (YK) and verified by one of the co-authors (ND).

Finally, the Cochrane Risk of Bias Tool was employed to assess the risk of bias. Disagreements throughout this process were resolved by consensus. When needed data was not directly found in the published articles, we obtained such data from the authors through response letters/e-mail or via reviewing their supplemental reports.

Defining Outcomes. ALL PVR was surgical. Ventricular arrhythmias were defined as postoperative (occurring after the first 3 postoperative months from initial PVR), sustained (>30 seconds), and associated with hemodynamic compromise. All ventricular arrhythmias were seen on ECG, Holtor monitoring, or telemetry.. In our study, we are examining the rate of arrhythmias in patients with PVR compared to patients with either no PVR or patients after PVR.

Meta-Analysis. The Hartung-Knapp-Sidik-Jonkman (HKSJ) method was employed to complete the statistical data using MedCalc software with: 1) a summary of data from individual studies; 2) an investigation of the studies heterogeneity graphically and statistically; 3) calculation of clustered indexes; 4) exploration of heterogeneity; and 5) graphical illustration via Forest Plots. Our assumption of heterogeneity was tested for each planned analysis using the Cochrane-Q heterogeneity and I^2 statistics with each of the following values: low 0-25%, moderate 25-75%, and high >75%. Random effects models using the Mantel-Haenszel method and fixed effects models were used. Meta-regression was analyzed using a generalization of Littenberg and Moses Linear model weighted by inverse of the variance or study size or unweighted. A secondary analysis was performed using the Der Simonian & Laird method and fixed effects models through Comprehensive Meta-Analysis software (Appendix A).

Results:

Study Selection and Patient Characteristics. The study selection process is presented in Figure 1.

Our initial literature search yielded 4,029 potential studies for review. Following exclusion of review articles, case reports, retrospective studies, abstracts, studies with insufficient data, and articles with overlapping study populations and redundant data, a total of 12 studies were included in the final analysis (Table 1). The characteristics of these 12 studies are presented in Table 1. All studies were conducted in the USA, Europe, Canada, and South Korea**.** The number of patients in each study varied with over 300 patients in the largest study to 18 patients in the smallest study, but all studies provided statistically significant data. Among 1,714 patients included in the analysis, 55% were men and 45% women with a weighted mean age of 31 years.

Ventricular arrhythmias were reduced by 60% in patients with PVR versus patients without PVR (OR 0.40, 95% CI 0.219-0.725, p <0.003) [Figure 2]. Similar results were noted in both fixed and random effect models. There was evidence for important heterogeneity of treatment effect among the studies for RV EF. I^2 was 60% indicating moderate heterogeneity (between 25% to 75%). This could be explained by the difference in cohorts at baseline, difference in duration of follow up, and different sample sizes. To account for this heterogeneity, we used both fixed and random models which showed very similar results.

The standardized difference in means for RV-EF after PVR reported in Figure 3A. There was no statistically significant difference in mean RV-EF after PVR (random-effects model: 0.018, SE = 0.092, p-value <0.845). There was evidence for important heterogeneity of treatment effect among the studies for RV EF. I^2 was 82% indicating considerable heterogeneity (>75%). This could be explained by the difference in cohorts at baseline, difference in duration of follow up, and different sample sizes. To account for this heterogeneity, we used both fixed and random models which showed very similar results.

The standardized difference in means for QRS duration after PVR is reported in Figure 3B. The overall difference in means of QRS did show a statistically significant reduction after PVR (random-effects model: -0.251, SE = 0.058, p < 0.0001). This means that QRS decreased and improved following PVR. There was evidence for important heterogeneity of treatment effects among the studies for QRS. Patients with a reduction in QRS duration following. I^2 was 98% indicating considerable heterogeneity (>75%). This could be explained by the difference in cohorts at baseline, difference in duration of follow up, and different sample sizes. To account for this heterogeneity, we used both fixed and random models which showed very similar results.

The standardized difference in means for RV Volume/RV-EDV after PVR is reported in Figure 3C. The overall difference in means of RV-EDV did show a significant reduction after PVR (random-effects model: -1.44, SE = 0.188, p < 0.0001). This means that RV-EDV increased and improved following PVR.There was evidence for important heterogeneity of treatment effect among the studies for RV-EDV. I^2 was 67% indicating moderate heterogeneity (between 25% to 75%). This could be explained by the difference in cohorts at baseline, difference in duration of follow up, and different sample sizes. To account for this heterogeneity, we used both fixed and random models which showed very similar results.

With regards to pre-operative RV-EDV, we observed statistically significant coefficients for changes in post-operative RV-EF and postoperative QRS (Figure 4) but not VT using meta regression analyses. This meant that patients with large volumes of RV-EDV prior to PVR experienced the greatest changes in RV-EF and QRS following PVR, but the preoperative RV-EDV did not impact the rate of ventricular arrhythmias following PVR. Similarly for pre-operative QRS duration, we observed statistically significant coefficients for changes in post-operative RV EF and RV-EDV but not VT (Figure 4). This meant that patients with longer QRS intervals prior to PVR experienced the greatest changes in RV-EF and QRS following PVR, but the preoperative QRS did not impact the rate of ventricular arrhythmias following PVR.

To ensure no publication bias, we performed multiple Funnel plot analyses [Appendix C]. Each funnel plot demonstrates symmetry around the central axis for the treatment group ($p < 0.05$ by Begg and Mazumdar's test or Egger's test). This means that there was minimal publication bias for our analyses.

Discussion:

In this meta-analysis, patients with repaired TOF with PVR have less ventricular arrhythmias compared to patients without PVR. Also, patients with greater preoperative RV-EDV and QRS duration did not have statistically significant reductions in ventricular arrhythmias after PVR.

TOF is the most common cyanotic congenital heart disease worldwide.[1,2]Indications for pulmonary valve replacement for these patients are severe pulmonary valve regurgitation with one of the following additional criteria: the presence of sustained atrial and ventricular arrhythmias, moderate tricuspid regurgitation, RV outflow tract obstruction, decreased performance capacity on exercise testing, or right ventricular dysfunction.[3–5]Despite these recommendations, the level of evidence remains low for PVR. There is currently no consensus in the guidelines on the exact timeline of PVR and how this would impact mortality.[8,9,11]Furthermore, although the risk of atrial arrhythmias is well established, ventricular arrhythmias were not well studied until patients had a longer survival and therefore a greater chance for mortality from sudden cardiac death.

A significant number of patients experience adverse events after initial TOF repair, such as ventricular arrhythmias.[12]The risk factors for increased ventricular arrhythmias for patients with TOF repair include the following: older age (>1 year old) at time of intracardiac repair, increased right ventricular systolic pressure, moderate or severe pulmonary regurgitation, ventricular dysfunction, increased cardiopulmonary bypass time, and a QRS duration >180 ms.[1,12–15]Mortality for these patients is often due to sudden ventricular arrhythmias, most often due to underlying pulmonary regurgitation and sudden death is the most common cause of death.[12,13,15]Sustained monomorphic ventricular tachycardia is the most clinically significant arrhythmia following PVR. If the pulmonary valve can be replaced, then theoretically the risk and incidence of ventricular arrhythmias is substantially decreased. PVR may decrease ventricular arrhythmias by reducing or eliminating pulmonary regurgitation that is associated with more ventricular arrhythmias. Hypothetically, right ventricular myocardial stretch increases electrical activity; right ventricular scar tissue from prior ventriculotomy creates areas of slowed ventricular activation; and right atrial dilation prolongs both the QRS and atrial refractoriness.[6]Previously implantable cardiac defibrillators (ICDs) were proposed for all patients with TOF to prevent ventricular arrhythmias. However, though there were high rates of appropriate and effective shocks, there was also a high level of inappropriate shocks and late lead-related complications.[16]Also, patients with EPS-guided, preoperative risk assessment for patients at high-risk for ventricular arrhythmias and subsequent empiric VT cryoablation with PVR unfortunately continued to have higher rates of inducible VT.[17]This study reveals that independently of QRS, patients with PVR had a 60% reduction in the incidence of ventricular arrhythmias. PVR could potentially be a very useful alternative to ICD implantation or VT cryoablation for this patient population.

The most important risk factors for the development of ventricular arrhythmias are the QRS duration, PR interval, clinical functional status, and RV hemodynamics. Several studies have shown that a QRS duration >180 ms, either preoperatively or postoperatively, as well as a lack of QRS narrowing after PVR were associated with significantly more sudden cardiac death from ventricular arrhythmias [9]. Additionally, patients with a QRS >180 ms have a 42-fold increased risk of developing sustained ventricular tachycardia and a 2.2-fold increased risk of sudden cardiac death during a 10-year follow-up, a very high-risk level.[11,18,19]Stabilization of the QRS complex may be lead to a decreased incidence of ventricular arrhythmias. Our study shows that QRS duration significantly decreased following PVR, but patients with decrease in QRS duration following PVR did not have a lower incidence of ventricular arrhythmias. This means that the QRS was not associated with the rate of ventricular arrhythmias, but PVR itself, regardless of echocardiogram or ECG parameters, reduced ventricular arrhythmias. The QRS may not be a useful marker for predicting ventricular arrhythmias after PVR.

Finally, prevention of progressive RV dilation and dysfunction is a major reason for advising PVR even in the absence of symptoms.[20,21]Several studies have confirmed that RV volume, when measured by cardiac MRI, improves after PVR.[22,23]There was a consensus that once pre-operative RV volume was >170 ml/m^2 and RV end-systolic volume (RVESV) was >85 ml/m^2, RV remodeling would be irreversible. Then PVR would not benefit the patients.[23]With cumulative RV dysfunction, the risk of ventricular arrhythmias is

significantly higher. The highest incidence of ventricular arrhythmias has been seen in patients undergoing TOF repair at older ages.[14]This may be due to the increase in the time required for RV remodeling with RV dilation and RV dysfunction. Because the end-diastolic (ED) and end systolic (ES)-RV dimensions will likely decrease after PVR, the RVEF value of 40% is predictive of post-operative outcomes.[6] Whether patients are symptomatic or asymptomatic, the RV dimensions have been reported to be more important for timing of PVR.[16] Our study showed a statistically significant reduction in RV-EDV and increase in RV EF, but these parameters did not correlate to the rate of ventricular arrhythmias.

Risk of bias and limitations. We acknowledge several limitations associated with this study. Because this is a study-level analysis, it is not possible to make definitive conclusions about individual incidence of ventricular arrhythmias. We identified only 12 randomized, prospective, and retrospective studies accounting for overall small sample size. As a result, our confidence interval is rather large but nonetheless it did reach statistical significance. This meta-analysis included data from non-randomized and/or observational studies which reflect real clinical data, but they are limited by treatment bias, confounders, and a tendency to overestimate treatment effects. All pulmonic valves were surgically replaced, so it would be interesting to analyze patients with transcutaneous pulmonic valve replacement in the future. The included studies had different cohorts of TOF patients with a diverse age range, but all patients had surgical repair of TOF early in childhood. Ideally, we would have analyzed all studies with similar cohorts, but there are very few and limited studies on TOF patients and ventricular arrhythmias as well as the impact of PVR.

We were not able to pinpoint one specific pathophysiology of ventricular arrhythmias due to TOF; however, detailed electrophysiological studies in the future may reveal new mechanisms for ventricular arrhythmias.

Conclusion:

For TOF survivors after initial repair, there was a markedly lower rate of ventricular arrhythmias in patients who received PVR compared to patients without PVR. Preoperative and postoperative echocardiogram parameters (RV-EDV, RV-EF) and the ECG parameter QRS were not associated with the rate of ventricular arrhythmias. Based on these data, it may be reasonable to consider PVR to reduce the incidence of ventricular arrhythmias in cardiac survivors of TOF. PVR could potentially be a very useful alternative to ICD implantation or VT cryoablation for this patient population.

Figures

FIGURE 1: PRISMA FLOW CHART OF STUDIES SCREENED AND INCLUDED IN META-ANALYSIS

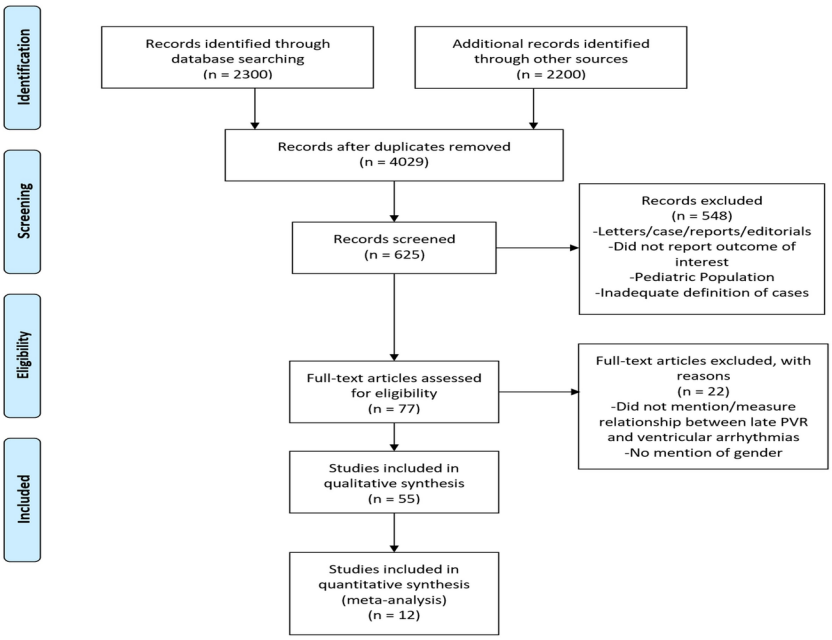


Table 1: Characteristics of Included Studies **Author and Publication Year**	*Table 1: Characteristics of Included Studies* **Country**	*Table 1: Characteristics of Included Studies* **Duration**	*Table 1: Characteristics of Included Studies* **Sample (N)/control [PVR, non-PVR]**	*Table 1: Characteristics of Included Studies* **Sex, Male and Female**	*Table 1: Characteristics of Included Studies* **Mean or Median Age at Initial Repair (years)**	*Table 1: Characteristics of Included Studies* **Mean age at date of PVR (years)**	*Table 1: Characteristics of Included Studies* **Mean time from complete repair to date of PVR (years)**	*Table 1 Characteristics of Included Studies* **Mean time fr date of PVR t date of last follow- (years)**
Buechel 2005, retrospective study	Switzerland	2 years	40	N/A	1.9 +/- 1.1	N/A	N/A	N/A
Gengaskul 2007, retrospective study	Canada	30 years	164 (82, 82)	41, 41; 45, 37	9+/-6.8, 7.3+/- 5.3	27.9+/- 13.1, 26.7+/- 12.1	18.9+/- 10, 19.5+/- 9.9	8/8+/- 7.5, 8.7+/- 7.3

Harrild 2008, retrospective study	USA	15 years	175 (98, 77)	N/A	1.3 (0-27.1), 2.9 (0-28.4)	24.6	19.7	25.5 (7.2-59. 25.8 (7.2-60.
Harrison 1997, retrospective study	Canada	4 years	18 (14, 4)	14, 4	9.3+/-7, 9.2+/-7	N/A	N/A	33.2+/- 10.9, 30.7+/- 10.4
Karamlou 2006, retrospective study	Canada	36 years	324 (75, 249)	49 (65%); 95 (55%)	8.6 (0.9-40), 5.4 (0-56)	37.7 (11.1-62.3) (included all reoperations)	26.1 (6.6-45.4)	N/A
Lee 2012, retrospective study	South Korea	13 years	170	103 (61%), 67 (39%)	2 (0.2-44.1)	16.7 (4.6-60.2)	13.8 (4.0-27.5)	N/A
Oosterhof 2007, prospective	Netherlands	13 years	71	42 (59%), 29 (41%)	5 (2.7-7.4)	29 (23-37)	14	N/A
Rizk 2020, retrospective study	Germany	12 years	434 (114, 320)	247 (57%), 187 (43%)	1.5 years (0.6-5)	N/A	N/A	N/A
Rotes 2015, retrospective study	Spain	12 years	221 (16, 205)	N/A	6.8 (4.2-12), 4.5 (2.2-7.6)	40.2 (26.6-55.3), 31.6 (19.7-45.1)	33.4, 27.1	N/A
Scherptong 2019, prospective study	Netherlands	5.5 +/- 3.5 years	180 (90, 90)	53 (59%), 37 (41%)	5.8 +/0 5.5	31.4 +/- 10.3	25.6	N/A
Therrien 2001, retrospective study	Canada	10 years	137 (67, 70)	33 (47%); 18 (60%)	9.7 +/- 8.2, 9.4 +/- 8	37.8 +/- 11/9	18.1 +/- 8.3	N/A

Vilegen 2002, prospective study	Netherlands	9 years	52		15 (58%), 11 (42%)	5.0 +/-	29.2 +/- 9	17.2	7.4 +/- 2.4	

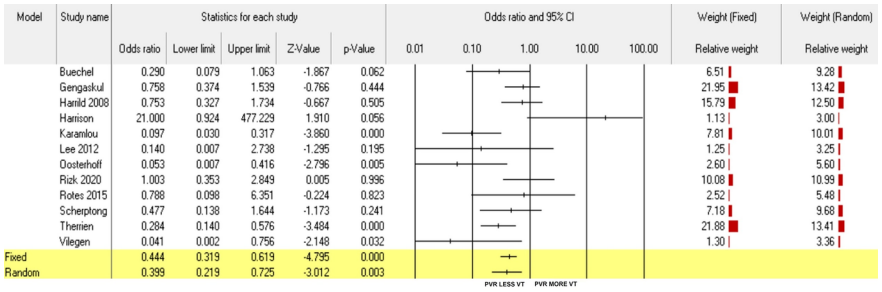
"Incompetence, Pulmonary Valve") AND ("Ventricular Arrhythmias, Ventricular Tachycardia, Arrhythmias").

Table 2: RV Echocardiographic Parameters and QRS both before and after PVR **Author**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **n, RV size/dilation before (PVR, control)**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV size/dilation after**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV EF before**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV EF after**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV systolic P before**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV systolic P after**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV volume before**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **RV volume after**	*Table 2: RV Echocardiographic Parameters and QRS both before and after PVR* **QRS before**
Buechel 2005, retrospective study	N/A	N/A	46.9 +/- 7.3	44.6 +/- 9.0	N/A	N/A	189.8 +/- 33.4	108.7 +/- 25.8	150 +/- 18
Gengaskul 2007, retrospective study	43 (68), 44 (15)	23 (78), 29 (73)	38+/- 9% (19), 45+/- 6% (9)	28 (38+/- 10%), 17 (40+/- 7%)	51+/- 18 (54), 41+/- 12 (37)	46+/- 11 (72), 39 +/- 12 (65)	283+/- 84 (17), 177+/- 83 (8)	194+/- 45 (28), 263+/- 63 (17)	72 (164+/- 21), 79 (147 +/-26)
Harrild 2008, retrospective study	Moderate (mild 3, mod 11, sev 13), moderate	Mild (none 6, mild 11, mod 6, sev 4)	46 (10), 50 (8)	45 (12)	N/A	N/A	196 (76), 132 (38)	131 (45)	158 (86-224), 148 (82-200)

Harrison 1997, retrospective study	N/A	N/A	N/A	N/A	47.9 +/- 20.8	N/A	N/A	N/A	N/A
Karamlou 2006, retrospective study	N/A	N/A	N/A	N/A	46 +/- 15	N/A	N/A	N/A	180+/- 22, 150+/- 29
Lee 2012, retrospective study	N/A	N/A	48 +/- 10	53 +/- 8	N/A	N/A	166 +/- 41	103 +/- 25	145 +/- 29
Oosterhof 2007, prospective	N/A	N/A	42 +/-10	43 +/- 10	N/A	N/A	171 +/- 44	119 +/- 34	155 +/- 29
Rizk 2020, retrospective study	N/A	N/A	46 +/- 10	53 +/- 9	N/A	N/A	129 +/-47	107 +/- 34	N/A
Rotes 2015, retrospective study	Moderate >11 (13, 107)	N/A	42 +/- 8	N/A	N/A	N/A	175 +/- 45	N/A	170 (160-198), 159 (138-176)
Scherptong 2019, prospective study	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	158 +/-29
Therrien 2001, retrospective study	Moderate >11 (47/70)	Moderate >11 (20/67)	N/A	N/A	>2/3 (12/70)	>2/3 (1/67)	N/A	N/A	178 +/- 30
Vilegen 2002, prospective study	N/A	N/A	41.7 +/- 9.7	42.1 +/- 11.1	N/A	N/A	166.8 +/- 40.3	114.3 +/- 35	N/A

Figure 2: SUMMARY FOREST PLOT OF CUMULATIVE INCIDENCE OF VENTRICU-

LAR ARRHYTHMIAS IN PATIENTS WITH PVR VERSUS PATIENTS WITHOUT PVR VIA FIXED AND RANDOM EFFECTS



Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	12	0.444	0.319	0.619	-4.795	0.000	27.755	11	0.004	60.368	0.563	0.450	0.202	0.750
Random	12	0.399	0.219	0.725	-3.012	0.003								

Relative risk, confidence interval and weight of studies for ventricular arrhythmias for patients treated with PVR versus patients without PVR. Test for heterogeneity of studies. The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio

FIGURE 3A-3C: SUMMARY FOREST PLOT OF CUMULATIVE RV-EF (3A), QRS (3B), RV VOLUME/RV-EDV (3C) IN PATIENTS WITH PVR VERSUS PATIENTS WITHOUT PVR VIA FIXED AND RANDOM EFFECTS

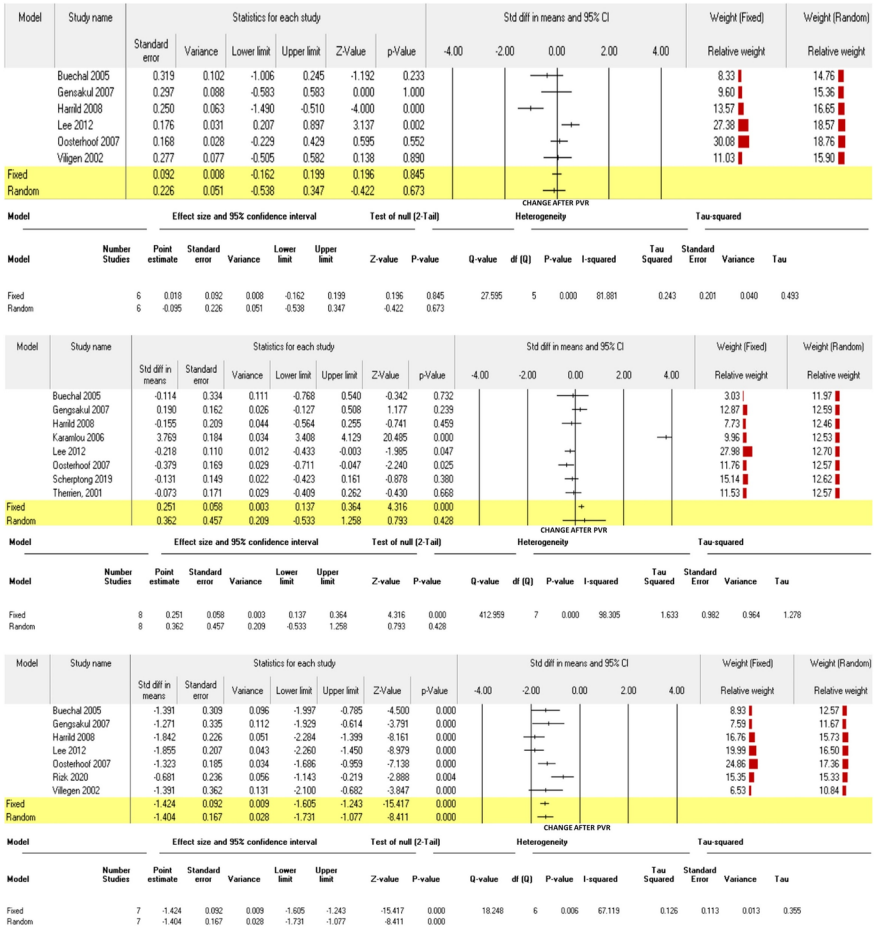
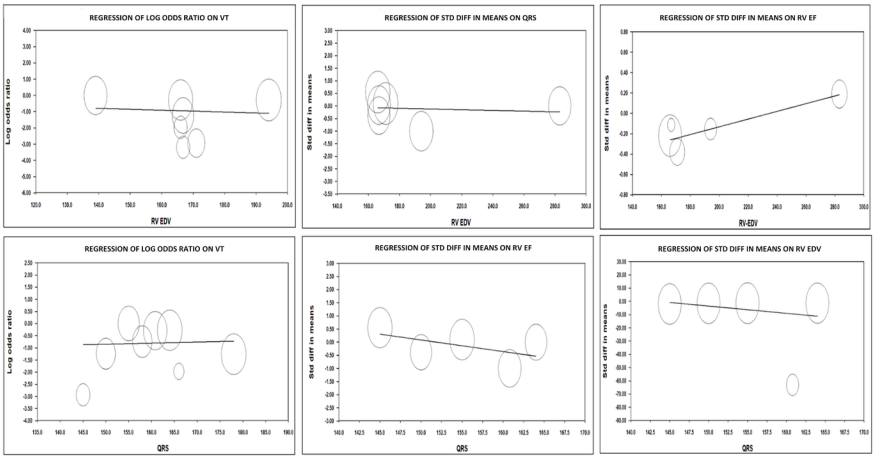


Figure 3A: Relative risk, confidence interval and weight of studies for RV EF volume for patients treated with PVR versus patients without PVR. Test for heterogeneity of studies. The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio.

Figure 3B: Relative risk, confidence interval and weight of studies for QRS for patients treated with PVR versus patients without PVR. Test for heterogeneity of studies. The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio.

Figure 3C: Relative risk, confidence interval and weight of studies for RV-EDV/RV volume for patients treated with PVR versus patients without PVR. Test for heterogeneity of studies. The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio.

FIGURE 4: Meta Regression by pre-op RV-EDV and pre-op QRS



Correlation between a given factor (plotted as a mean or proportion of that factor on the x-axis), in this graph pre-op RV-EDV, and the effect of PVR on the outcome (plotted on the y-axis). Each circle in the plot represents a study, and the circumference of each circle is proportional to study population size. (A) Incidence of ventricular arrhythmias (B) RV-EF and difference in means (C) QRS and difference in means. Correlation between a given factor (plotted as a mean or proportion of that factor on the x-axis), in this graph pre-op QRS, and the effect of PVR on the outcome (plotted on the y-axis). Each circle in the plot represents a study, and the circumference of each circle is proportional to study population size. (A) Incidence of ventricular arrhythmias (B) RV-EF and difference in means (C) RV-EDV and difference in means.

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APPENDIX A: OTTAWA SCALES

Supplemental Table 1: Newcastle-Ottawa scale for included studies.

Publication	Year	Newcastle-Ottawa Scale								
		Selection				Comparability	Outcome			Total
		Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome demonstration at start		Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow-up	
Buechel	2005	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Gengaskul	2007	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Harrild	2008	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Harrison	1997	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Karamlou	2006	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Lee	2012	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Oosterhoff	2007	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Rizk	2020	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Rotes	2015	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Scherptong	2019	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Therrien	2001	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Vilegen	2002	✱	✱	✱	✱	✱✱	✱	✱	✱	9

The Newcastle-Ottawa Scale (NOS) evaluates the included studies based on selection, comparability and outcome. The maximum score for each criterion is 4, 2 and 3, respectively, with the maximum total score equaling 9.

Supplemental Table 2: Quality data for eligible data sets.

Publication	Year	Objective defined	Outcome described	Characteristics described	Confounders described	Main findings outlined	Heterogeneous population	Individuals generating data blinded to outcomes	Reproducibility assessed	Recruiting all subjects over same time period
Buechel	2005	Yes	Yes	Yes	Yes	Yes	No	NS	Yes	Yes
Gengaskul	2007	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Harrild	2008	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Harrison	1997	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Karamlou	2006	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Lee	2012	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Oosterhoff	2007	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Rizk	2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Rotes	2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Scherptong	2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Therrien	2001	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Vilegen	2002	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

NS = not specified.

Appendix B: I^2 and Q for Meta-Regressions

For VT by RV EDV

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.0563	4.1699	-8.1166	8.2292	0.01	0.9892
RV EDV	-0.0060	0.0247	-0.0544	0.0425	-0.24	0.8095

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.06, df = 1, p = 0.8095
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.7244, Tau = 0.8511, I^2 = 59.36%, Q = 12.30, df = 5, p = 0.0309

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.4048, Tau = 0.6362, I^2 = 51.25%, Q = 12.31, df = 6, p = 0.0554
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.79)

Number of studies in the analysis 7

For RV EF by RV-EDV

Main results for Model 1, Random effects (MM), Z-Distribution, Std diff in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.1602	1.1282	-2.0510	2.3714	0.14	0.8871
RV EDV	-0.0014	0.0058	-0.0127	0.0100	-0.23	0.8153

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.05, df = 1, p = 0.8153
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.2775, Tau = 0.5268, I^2 = 84.60%, Q = 25.98, df = 4, p = 0.0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.2433, Tau = 0.4933, I^2 = 81.88%, Q = 27.60, df = 5, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.14)

Number of studies in the analysis 6

For QRS by RV EDV

Main results for Model 1, Random effects (MM), Z-Distribution, Std diff in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-0.8890	0.3184	-1.5130	-0.2650	-2.79	0.0052
RV-EDV	0.0038	0.0016	0.0007	0.0069	2.38	0.0174

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 5.65, df = 1, p = 0.0174
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.0000, Tau = 0.0000, I^2 = 0.00%, Q = 1.00, df = 3, p = 0.8016

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.0198, Tau = 0.1407, I^2 = 39.86%, Q = 6.65, df = 4, p = 0.1555
Proportion of total between-study variance explained by Model 1
R^2 analog = 1.00

Number of studies in the analysis 5

for VT by QRS

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	-1.5876	4.8568	-11.1068	7.9315	-0.33	0.7438
QRS	0.0049	0.0300	-0.0539	0.0637	0.16	0.8696

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 0.03, df = 1, p = 0.8696
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.3041, Tau = 0.5514, I^2 = 49.66%, Q = 11.92, df = 6, p = 0.0638

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.2157, Tau = 0.4645, I^2 = 43.34%, Q = 12.35, df = 7, p = 0.0895
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.41)

Number of studies in the analysis 8

for RV EF by QRS

Main results for Model 1, Random effects (MM), Z-Distribution, Std diff in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	6.6650	5.1010	-3.3328	16.6628	1.31	0.1913
QRS	-0.0438	0.0329	-0.1084	0.0207	-1.33	0.1833

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 1.77, df = 1, p = 0.1833
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.2004, Tau = 0.4477, I^2 = 78.78%, Q = 14.13, df = 3, p = 0.0027

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.3010, Tau = 0.5486, I^2 = 85.50%, Q = 27.59, df = 4, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.33

Number of studies in the analysis 5

for RV EDV BY QRS

Main results for Model 1, Random effects (MM), Z-Distribution, Std diff in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	77.7597	27.6084	23.6483	131.8711	2.82	0.0049
QRS	-0.5410	0.1791	-0.8921	-0.1899	-3.02	0.0025

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 9.12, df = 1, p = 0.0025
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 6.6928, Tau = 2.5871, I^2 = 98.66%, Q = 223.37, df = 3, p = 0.0000

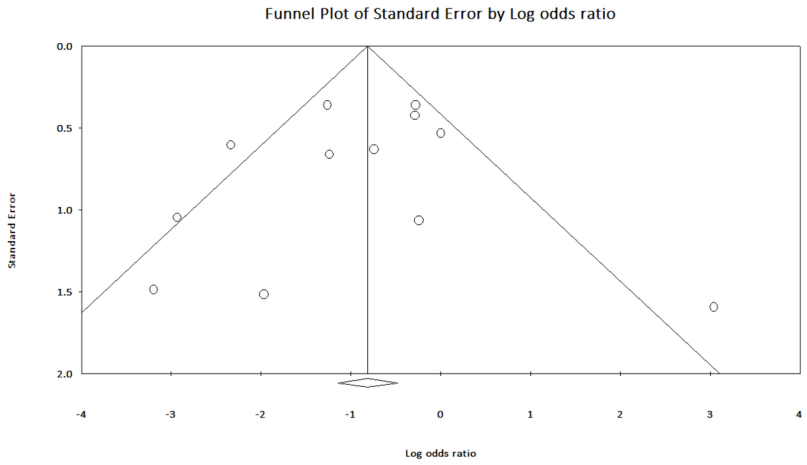
Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 4.4239, Tau = 2.1033, I^2 = 98.22%, Q = 224.90, df = 4, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.00 (computed value is -0.51)

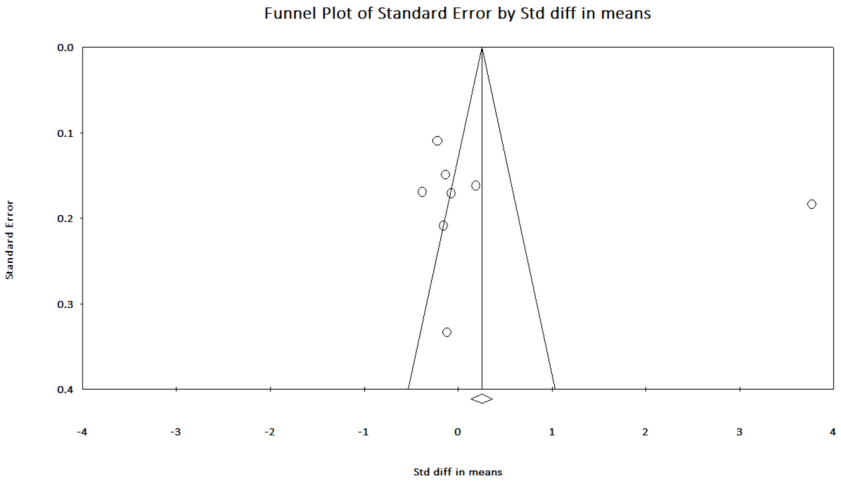
Number of studies in the analysis 5

Appendix C: FUNNEL PLOTS

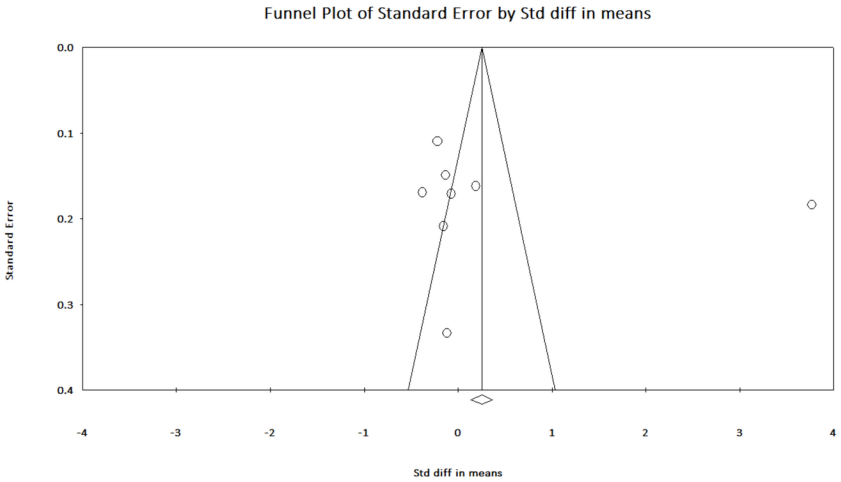
For VT



For RV EF



For QRS



For RV EDV